# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074835

## BIOEQUIVALENCE REVIEW(S)

ANDA 74-835

JUN 12 1996

Invamed Inc.
Attention: Mahendra B. Patel, Ph.D.
2400 Route 130
Dayton NJ 08810

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Nortriptyline Hydrochloride Capsules USP, 10 mg, 25 mg, 50 mg and 75 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 500 mL of water at 37°C using USP apparatus I basket at 100 rpm. The test product should meet the following specifications:

   Not less tha(b)4of the labelled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

(b)4 - Confidential

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 10 1996

Nortriptyline
75 mg Capsule
50 mg Capsule
25 mg Capsule
10 mg Capsule
ANDA # 74-835
Reviewer: A. J. Jackson
WP #74835SDW.196

Invamed Inc.
Dayton, NJ
Submission Dated:
January 13, 1996

Review of Fasting 75 mg Bioequivalence Study and Request for Waiver for 50 mg, 25 mg and 10 mg Tablets

Background

Nortriptyline hydrochloride is a dibenzocycloheptene-derivative tricyclic antidepressant drug which is the active metabolite of amitriptyline. Nortriptyline is indicated for the relief of symptoms of depression. The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Nortriptyline hydrochloride is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. Studies suggest that nortriptyline interferes with the transport, release, and storage of catecholamines.

Following oral administration, peak plasma concentrations occur within 7-8.5 hours. The plasma half-life of nortriptyline ranges from 16 to more than 90 hours.

The reference product is Pamelor® manufactured by Sandoz. It is supplied as 75 mg, 50 mg, 25 mg and 10 mg capsules.

Objective:

The aim of this study is to compare the oral absorption of nortriptyline hydrochloride capsules manufactured by Invamed Inc. with a commercial lot of the reference product, Pamelor® capsules manufactured by Sandoz Pharmaceuticals following a single 75 mg dose.

Methods:

The study was conducted by [redacted] (b)4 - Confidential [redacted] under the direction of [redacted] Samples were analyzed at [redacted] (b)4 - Confidential Business [redacted] under the direction of [redacted] Period I study dates were July 8-15, 1995, while those for period II were July 29-August 5, 1995.

I. Characterization of Study Group:

A. Inclusion criteria:

1. 34 male volunteers were selected for this study. Male volunteers were between the ages of 18 and 40 years. Weight range of the volunteers was within ±10% of normal body weight relative to height and frame size as described in the 1983 Metropolitan Height and Weight Table.

2. Each volunteer was given a general physical examination within 14 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV 1&2 antibody screen, hepatitis B surface antigen screens. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram.

4. No known allergy to nortriptyline.

5. Abstenance from caffeine and/or xanthine-containing products at least 48 hours prior to study days.

6. Abstaining from alcoholic products for at least 48 hours before dosing is scheduled.

B. Exclusion Criteria:

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma.

2. Any noted EKG abnormality.

3. Hypersensitivity to nortriptyline.

4. Volunteers who had taken any drug known to induce or inhibit hepatic drug metabolism in the 30 days prior to period I dosing.

5. Participation in a previous clinical trial or the donation of one pint or more of blood within the past 30 days.

6. Use of any OTC medication on a regular basis.

7. Positive screen for drugs of abuse.

8. Positive HBsAg or HIV screen.

9. Subjects that smoke.

10. Use of a drug therapy known to induce or inhibit hepatic drug metabolism.

C. Informed Consent:

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

A total of 34 subjects were enrolled in the study. There were no subject drop outs.

A. Subjects fasted 10 hours overnight until 4.0 hrs after their scheduled dosing times. Water was not allowed from 1 hour before until 2 hours after dosing but was allowed ad lib thereafter.

Standard meals were provided at 4 hours after dosing.

B. The products employed in the study were:

1. Test: Invamed Inc. 75 mg nortriptyline capsules, Lot # D950502, Lot Size [redacted] capsules, Potency 99.5%.

2. Reference product: Sandoz 75 mg Pamelor® capsules, Lot # 183W7484, expiration date January 2000, Potency 102%.

There was a 21 day washout between doses.

The formulation for the 75 mg test product was:

| | |
|---|---|
| Nortriptyline Hydrochloride USP 23 | 85.385 mg/capsule |
| Pregelatinized starch NF 18 | (b)4 - Confidential Business |
| Silicon Dioxide,NF 18 | |
| Magnesium Stearate, NF 18 | |
| Total Fill Weight | |
| One unit of /hard gelatin capsule, size 1 | |
| Total weight: | 474.00 mg |

C. A 75 mg dose (1 x 75 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in table 1.

Table 1. Random Assignment of 34 subjects

| Sequence | SUBJECT |
|---|---|
| A,B | 1,3,4,6,7,8,9,14,15,16,17,25,26,27,32,33,34 |
| B,A | 2,5,7,11,12,13,18,19,20,21,22,23,24,28,29,30, 31 |

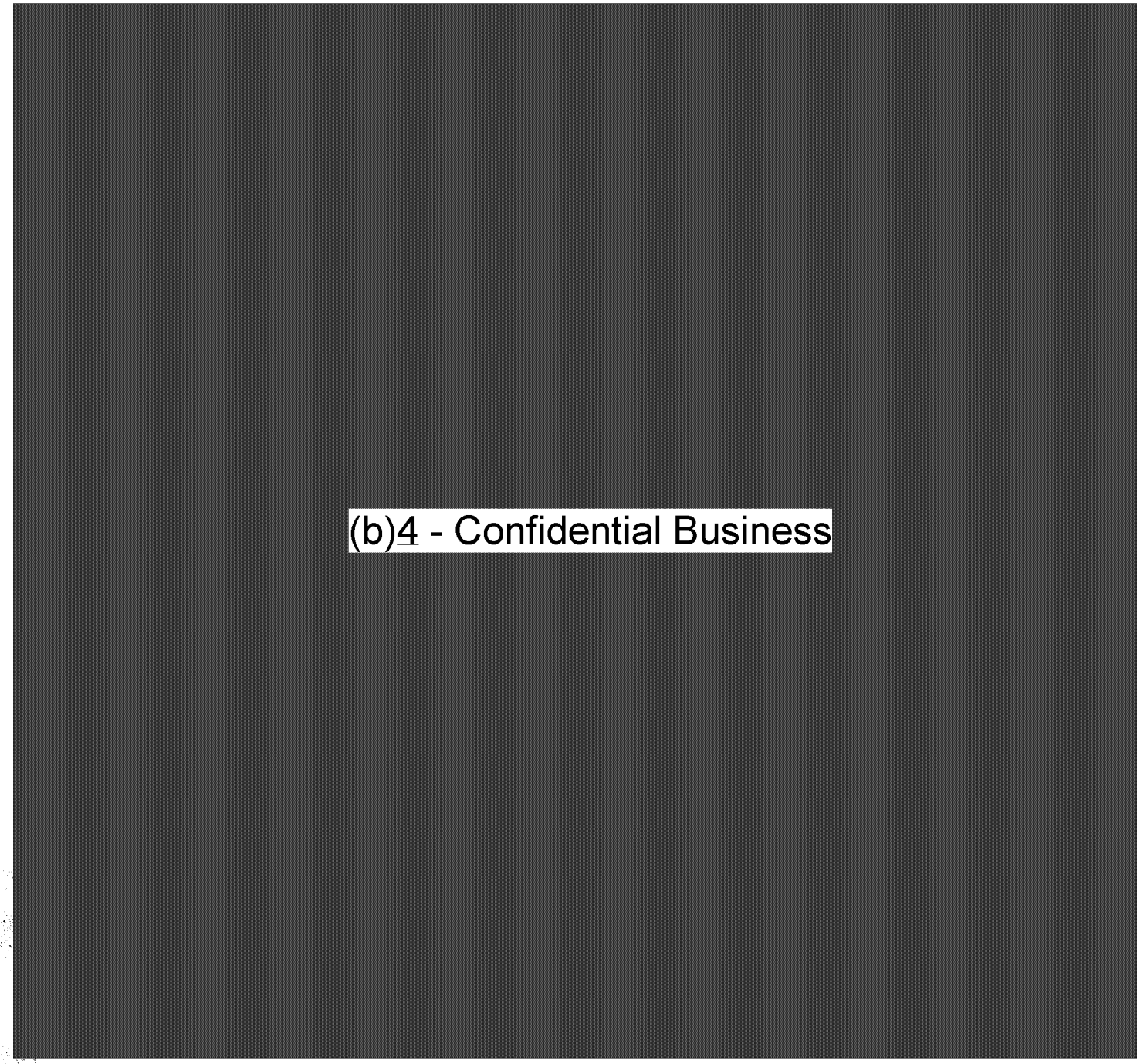
Treatment A: Nortriptyline capsules, 75 mg (1 capsule) Invamed

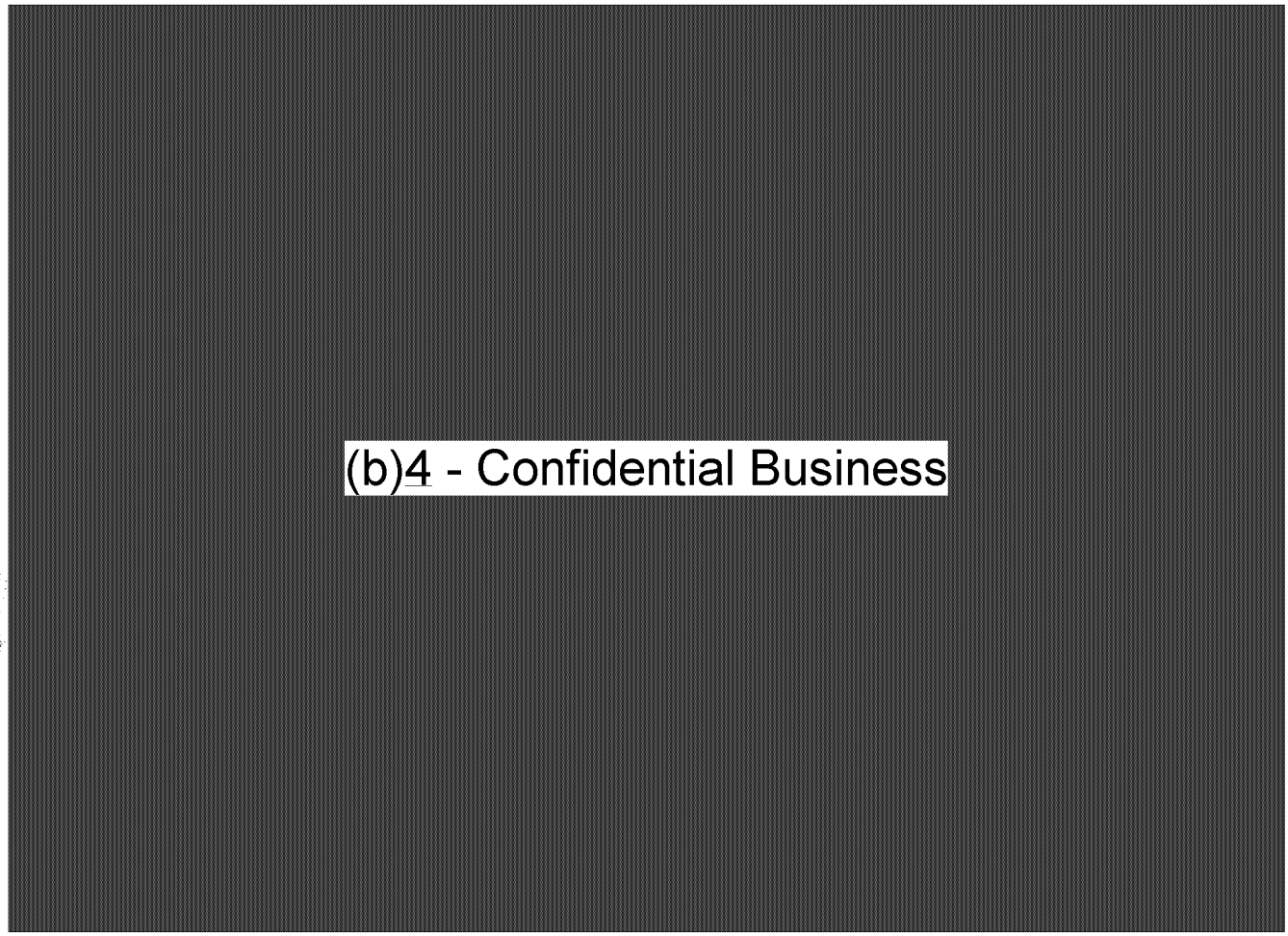
Treatment B: Pamelor® capsules, 75 mg (1 capsule) Sandoz Pharmaceuticals

D. Plasma samples were collected pre-dose and at the following times post-dose: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours.

E. A sitting blood pressure and radial heart rate were measured prior to dosing and at 4, 12, 24, and 48 hours after each dose.

III. Analytical






IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The 90% confidence intervals for the difference between formulations and the power to defect a 20% difference between formulations were calculated for each parameter based upon its ANOVA.

Log-transformed data was submitted for analysis.

## Results

Table 6. Nortriptyline mean plasma levels, ng/ml (±sd), for the subjects that received the test and reference formulations after an overnight fast.

| Time | Test | | Reference | |
|---|---|---|---|---|
| 0.00 HR | 0.000 | 0.000 | 0.000 | 0.000 |
| 1.00 HR | 2.268 | 1.321 | 1.713 | 1.1660 |
| 2.00 HR | 11.020 | 5.937 | 9.731 | 4.965 |
| 3.00 HR | 20.050 | 7.876 | 18.126 | 6.590 |
| 4.00 HR | 25.965 | 8.272 | 25.056 | 7.137 |
| 5.00 HR | 31.924 | 8.312 | 32.015 | 6.590 |
| 6.00 HR | 35.159 | 9.471 | 35.362 | 6.834 |
| 7.00 HR | 36.776 | 9.503 | 38.262 | 7.457 |
| 8.00 HR | 35.924 | 9.585 | 37.876 | 7.389 |
| 9.00 HR | 36.338 | 10.637 | 37.094 | 7.932 |
| 10.0 HR | 34.929 | 9.968 | 35.894 | 8.041 |
| 12.0 HR | 33.029 | 9.435 | 35.394 | 8.497 |
| 16.0 HR | 26.853 | 8.974 | 28.815 | 8.245 |
| 24.0 HR | 22.826 | 8.146 | 23.663 | 8.385 |
| 36.0 HR | 16.816 | 8.115 | 17.574 | 8.484 |
| 48.0 HR | 12.729 | 7.424 | 13.541 | 7.420 |
| 72.0 HR | 8.113 | 6.216 | 8.395 | 5.956 |
| 96.0 HR | 5.011 | 5.064 | 5.565 | 5.213 |
| 120 HR | 3.167 | 3.882 | 3.325 | 3.997 |
| 144 HR | 1.818 | 2.648 | 2.146 | 3.113 |
| 168 HR | 1.349 | 2.594 | 1.343 | 2.576 |

Table 7

Summary of Mean Bioavailability Parameters for Nortriptyline

| Test | | | Reference | | Ratio T/R |
|---|---|---|---|---|---|
| Variable Label | Mean | Std Dev | Mean | Std Dev | |
| AUCTLQC[1] ng/ml x hr | 1643.470 | 844.631 | 1729.395 | 859.907 | .95 |
| AUCINF[2] ng/ml x hr | 1773.758 | 1021.740 | 1868.034 | 1049.649 | .95 |
| CMAX ng/ml | 39.182 | 10.644 | 39.935 | 7.804 | .98 |
| TMAX hr | 7.735 | 1.943 | 7.794 | 1.737 | --- |
| KELM hr-1 | 0.025 | 0.009 | 0.026 | 0.009 | --- |
| THALF hr | 30.891 | 12.112 | 31.284 | 13.291 | --- |
| LAUCTLQC ng/ml x hr | 7.278[3] | 0.518 | 7.333 | 0.520 | .94[4] |
| LAUCINF ng/ml x hr | 7.338[3] | 0.539 | 7.394 | 0.538 | .94 |
| LCMAX ng/ml | 3.632[3] | 0.276 | 3.665 | 0.224 | .96 |

1.AUC to the last measurable plasma concentration
2.AUC to infinity
3.Mean of Ln
4.Ratio of Geometric Means

**The 90% confidence intervals were verified by the reviewer.**

Table 8. 90% Confidence Intervals

| Parameter | |
|---|---|
| LAUCTLQC | (91.0-98.4) |
| LAUCINF | (91.1-98.1) |
| LCmax | (92.6-101) |

Table 9

Mean (±) E-OH-Nortriptyline Plasma Levels ng/ml ± SD

| Time | Test | | Reference | |
|---|---|---|---|---|
| 0.00 HR | 0.000 | 0.000 | 0.000 | 0.000 |
| 1.00 HR | 6.485 | 5.240 | 5.604 | 6.432 |
| 2.00 HR | 22.795 | 16.437 | 22.320 | 16.529 |
| 3.00 HR | 31.348 | 21.329 | 31.808 | 21.668 |
| 4.00 HR | 34.548 | 22.510 | 34.969 | 22.303 |
| 5.00 HR | 36.748 | 23.026 | 37.353 | 22.538 |
| 6.00 HR | 35.027 | 20.549 | 36.143 | 20.942 |
| 7.00 HR | 34.266 | 20.801 | 35.559 | 19.908 |
| 8.00 HR | 33.048 | 19.485 | 35.061 | 19.203 |
| 9.00 HR | 31.643 | 18.004 | 33.389 | 18.341 |
| 10.0 HR | 29.752 | 16.335 | 31.360 | 16.517 |
| 12.0 HR | 27.245 | 14.636 | 28.809 | 14.616 |
| 16.0 HR | 21.378 | 11.136 | 22.624 | 11.159 |
| 24.0 HR | 17.465 | 8.456 | 18.155 | 8.309 |
| 36.0 HR | 11.049 | 4.708 | 11.787 | 4.954 |
| 48.0 HR | 8.486 | 3.528 | 8.872 | 3.638 |
| 72.0 HR | 4.829 | 2.206 | 5.028 | 2.050 |
| 96.0 HR | 2.631 | 1.519 | 2.893 | 1.443 |
| 120 HR | 1.455 | 1.267 | 1.481 | 1.081 |
| 144 HR | 0.606 | 0.972 | 0.714 | 0.897 |
| 168 HR | 0.310 | 0.794 | 0.323 | 0.594 |

Table 10

Summary of Mean (±) E-OH-Nortriptyline Bioavailability Parameters

| Variable Label | Mean | Std Dev | Mean | Std Dev | Ratio T/R |
|---|---|---|---|---|---|
| AUCTLQC[1] ng/ml x hr | 1198.979 | 508.614 | 1262.716 | 513.859 | 0.95 |
| AUCINF[2] ng/ml x hr | 1261.616 | 503.865 | 1319.493 | 497.364 | 0.96 |
| CMAX ng/ml | 38.019 | 22.969 | 38.997 | 22.250 | 0.97 |
| TMAX hr | 6.412 | 3.619 | 6.735 | 3.604 | --- |
| KELM hr-1 | 0.026 | 0.010 | 0.025 | 0.010 | --- |
| THALF hr | 32.357 | 17.645 | 33.288 | 17.279 | --- |
| LAUCTLQC ng/ml x hr | 6.954[3] | 0.606 | 7.006 | 0.621 | 0.95[4] |
| LAUCINF ng/ml x hr | 7.028 | 0.538 | 7.083 | 0.517 | 0.95 |
| LCMAX ng/ml | 3.359 | 0.895 | 3.394 | 0.897 | 0.96 |

1.AUC to the last measurable plasma concentration
2.AUC to infinity
3.Mean Ln
4.Ratio of Geometric Means

**The 90% confidence intervals were verified by the reviewer.**

Table 11. 90% Confidence Intervals

| Parameter | |
|---|---|
| LAUCTLQC | (91.9-99.0) |
| LAUCINF | (91.2-98.2) |
| LCmax | (91.2-102) |

Adverse Effects

Headache was the most frequently reported adverse effect which appeared to be equally distributed between test and reference products. The data is summarized in table 12.

Capsule Composition

The comparative formulations for the 75 mg, 50 mg, 25 mg and 10 mg capsules are presented in table 13(attached).

Dissolution

The dissolution study for nortriptyline hydrochloride was done as follows:

| | |
|---|---|
| Apparatus: | Basket, 100 RPM |
| Medium: | 500 ml Water |
| No. of Units Analyzed: | 12 |
| Specifications: | NLT (b)4 in 30 minutes |
| Assay: | (b)4 - Confidential |

Comments:

1. The 90% confidence intervals for the test product for the parameters LCmax, LnAUC(0-t) and LNAUC(0-inf) are with the acceptable limits of 80-125% of the reference product.

2. The 50 mg, 25 mg and 10 mg capsules are compositionally proportional to the 75 mg capsule.

3. The dissolution data are acceptable. The reference product was highly variable at the 10 min sampling time for the 75 mg, 50 mg and 25 mg capsules.

4. The firms dissolution specification of NLT (b)4 in 30 minutes should be changed to NLT (b)4 in 30 minutes to be consistent with USP 23.

Recommendation

1. The bioequivalence study conducted by Invamed on its 75 mg nortriptyline capsule, lot D950502 comparing it to Sandoz's Pamelor® 75 mg capsules has been found to be acceptable by the Division of Bioequivalence. Therefore, Invamed's 75 mg nortriptyline capsule is deemed bioequivalent to Pamelor®, 75 mg capsule, manufactured by Sandoz.

2. The in vitro dissolution testing conducted on the 75 mg strength (lot # D950502), 50 mg strength(lot # D950504), 25 mg strength (lot # D950505), and the 10 mg strength(lot # D950507) is acceptable. The formulations for the 50 mg, 25 mg and 10 mg capsules are compositionally proportional to the 75 mg capsule which underwent a bioequivalence study. The waiver of in vivo bioequivalence study requirements for the 50 mg, 25 mg, and 10 mg capsules is granted. Therefore, Invamed's 50 mg, 25 mg and 10 mg capsules are deemed bioequivalent to Pamelor®, 50 mg, 25 mg and 10 mg capsules, manufactured by Sandoz.

3. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of water at 37 C using USP apparatus I basket at 100 rpm. The test product should meet the following specifications:

   Not less than (b)4 of the labelled amount of the drug in the dosage form is dissolved in 30 minutes.

Andre J. Jackson /S/
Division of Bioeq
Review Branch I

RD INITIALLED YC HUANG /S/
FT INITIALLED YC HUANG Date: 5/31/96

Concur: /S/ Date: 6/10/96
Keith Chan, Ph.D.
Director,
Division of Bioequivalence

cc: ANDA 74-835 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File.

AJJ/042396/dbm/WP #74835SDW.196
1st Draft 04/22/96
2nd Draft 05/29/96

**Table 14. In Vitro Dissolution Testing**

Drug (Generic Name):Nortriptyline
Dose Strength:75 mg
ANDA No.:74-835
Firm:Invamed
Submission Date:January 13, 1996
File Name:74835SDW.196

I. Conditions for Dissolution Testing:

USP XXII Basket: x Paddle: RPM: 100
No. Units Tested: 12
Medium: Water Volume:500 ml
Specifications: NLT [redacted] in 30 min

Reference Drug: Pamelor
Assay Methodology: [redacted] (b)4 - Confidential

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot # D950502 Strength(mg) 75 | | | Reference Product Lot # 183W7484 Strength(mg) 75 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 10 | 74.4 | [redacted] (b)4 - Confidential Business | 11.8 | 73.7 | [redacted] (b)4 - Confidential Business | 17.9 |
| 20 | 95.7 | | 2.5 | 98.4 | | 2.1 |
| 30 | 96.1 | | 2.0 | 99.1 | | 1.6 |
| 40 | 96.3 | | 1.9 | 99.7 | | 1.5 |

| Sampling Times (Minutes) | Test Product Lot # D950505 Strength(mg) 25 | | | Reference Product Lot # 899W6908 Strength(mg) 25 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 10 | 84.7 | [redacted] (b)4 - Confidential Business | 3.1 | 32.3 | [redacted] (b)4 - Confidential Business | 18.1 |
| 20 | 91.4 | | 1.8 | 91.8 | | 2.0 |
| 30 | 92.1 | | 2.0 | 97.5 | | 1.3 |
| 40 | 92.4 | | 1.8 | 98.7 | | 1.3 |

. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot # D950504 Strength(mg) 50 | | | Reference Product Lot # 364W6969 Strength(mg) 50 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 10 | 82.0 | (b)4 - Confidential Business | 6.2 | 34.4 | (b)4 - Confidential Business | 16.9 |
| 20 | 93.5 | | 1.2 | 93.7 | | 2.4 |
| 30 | 94.2 | | 1.3 | 98.2 | | 0.9 |
| 40 | 94.9 | | 1.1 | 97.8 | | 0.9 |

| Sampling Times (Minutes) | Test Product Lot # D950507 Strength(mg) 10 | | | Reference Product Lot # 238X7230 Strength(mg) 10 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 10 | 90.9 | (b)4 - Confidential Business | 1.7 | 90.8 | (b)4 - Confidential Business | 7.9 |
| 20 | 93.1 | | 2.0 | 105.5 | | 2.7 |
| 30 | 93.6 | | 1.5 | 106.2 | | 2.2 |
| 40 | 94.0 | | 1.7 | 106.2 | | 2.2 |